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REMARKS

Claims 31-43, 45-56 and 58-60 are pending in the application. Claim 49 has been withdrawn. The following rejections are at issue and are set forth by number in the order in which they are addressed:

1. Claim 37 is objected to due to an informality;
2. Claims 31-43, 45-48, 50-56, and 58-60 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;
3. Claims 31-42, 45-48, 50-56 and 58-60 stand rejected under §112, first paragraph, as allegedly lacking an adequate written description;
4. Claims 50-53, 55, 56 and 58-60 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Srivastava (WO 97/10001);
5. Claims 50-56 and 58-60 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Multhoff et al. (U.S. 6,261,839);
6. Claims 31-37, 39-43, 45-48, 54-56 and 58-60 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Multhoff et al., Blood 86:1374-82 (1995), in view of Srivastava and Multhoff et al., J. Immunol. 158:4341-50 (1997) and the abstract of Boltzer et al., Cell Stress and Chaperones 3:6-11 (1998); and
7. Claims 55 and 56 stand rejected under the judicially created doctrine of double patenting over Claims 19 and 20 of U.S. Pat. No. 6,261,839.

Claims 31, 42, 50 and 55 have been amended in order to further define the present invention and to further the Applicant's business interests and the prosecution of the present application in a manner consistent with the PTO's Patent Business Goals (PBG; 65 Fed. Reg. 54603 (September 8, 2000), and not in acquiescence to the Examiner's arguments and while reserving the right to prosecute the original (or similar) claims in the future. Support for these amendments may be found in the specification at page 5, first full paragraph and page 11, second full paragraph, among other places.

1. The Informalities Have Been Corrected

Claim 37 is objected to due to an informality in that "an isolated" is recited twice. It appears that the Examiner actually meant to refer to Claim 31. Claim 31 has been amended accordingly.

2. The Claims are Definite

Claims 31-43, 45-48, 50-56, and 58-60 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner objects to the Applicants use of the term "derivative". As explained in their previous Response, Applicants vigorously assert that the use of the term "derivative" does not render the claims indefinite as it has been defined in the specification. Nevertheless, in order to further the business interests of the Applicants, the claims have been amended to delete the term "derivative". It is noted that this amendment in no way alters claims coverage with respect to use of Hsp70 proteins, polypeptides, and fragments thereof.

3. The Claims are Supported By an Adequate Written Description

Claims 31-42, 45-48, 50-56 and 58-60 stand rejected under §112, first paragraph, as allegedly lacking an adequate written description. In the first part of the rejection, the Examiner argues that the specification does not provide an adequate written description for the genus of "derivatives". This rejection is now moot.

In the second part of the rejection, the Examiner argues that the specification does not provide an adequate written description for the "70% homologous" genus. In support of this rejection, the Examiner argues the following:

> Thus the specification teaches that 70% homologous sequences encompasses amino acid sequences which have substitutions, deletions, and additions of amino acids from amino acid residues 384-681 of SEQ ID NO:1. No further description of any variant protein structure is made by the specification and no embodiment limiting the number of amino acid substitutions, deletions or additions is present in the specification or claims. Thus the scope of the genus includes numerous structural variants and the genus is highly variant because a significant number of structural differences between genus members is permitted. Neither the specification or claims indicate distinguishing structural and functional characteristics shared by members of the genus that could serve to distinguish proteins in the genus from other proteins not in the genus.
>
> The general knowledge and skill in the art do not supplement the omitted description of derivatives and proteins comprising variants or residues 384-681 of SEQ ID NO:1, and derivatives thereof, because specific, not general guidance is what is needed. Since the disclosure fails to identify the structural and functional attributes of the genuses, and because the genuses are highly variant, SEQ ID NO:1 alone is insufficient to describe the claimed genus. Furthermore, one of skill in the art would conclude that the specification also failed to describe a number of species representative of the "derivative" genus and the "70% homologous" genus. Thus, the applicant was not in possession of either the claimed "derivative" or "homolog" genuses.

Applicants respectfully submit that this ground of rejection is both factually and legally flawed. The Examiner's reasoning that neither specification nor the claims indicate distinguishing functional and structural characteristics is factually flawed because by citing SEQ ID NO:1 and polypeptides that have 70% or greater homology to amino acids 384-641 of SEQ ID NO.: 1 the applicants have indicated the **structure** of the proteins/polypeptides. Furthermore, the specification clearly indicates in the paragraph bridging pages 4 and 5 that computer programs can be used to determine the degree of homology to SEQ ID NO:1. Thus, the Examiner is factually mistaken in the argument that a person of ordinary skill in the art cannot determine members of the genus. To the contrary, persons of ordinary skill in the art of the invention routinely utilize programs such as BLASTP to determine homology between sequences and would thus recognize that the Applicants had possession of the claimed genus.

Perhaps more importantly, the Examiner's arguments are inconsistent with the very clear legal guidelines of both the Federal Circuit and the Patent Office. The Federal Circuit addressed the issue of what constitutes an adequate written description of protein and nucleic acid sequences in *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (1997). In particular, the Federal Circuit stated the following:

> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the *'525* patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel, 984 F.2d 1164, 1171, 25 U.S.P.Q.2D (BNA) 1601, 1606 (Fed. Cir. 1993).* Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the **DNA itself**." *Id. at 1170, 25 U.S.P.Q.2D (BNA) at 1606.*

Id. at 1567 (emphasis added). By basing the claims on SEQ ID NO:1 and sequences homologous to it, the Applicants have met the legal requirement of *Eli Lilly* to provide a description of the **sequence itself**. Thus, the Examiner's arguments that reference to SEQ ID NO:1 does not provide a distinguishing functional characteristic are wrong as a matter of law.

The Examiner's argument is also inconsistent with the USPTO's own guidelines for examination under the written description requirement. Recent Federal Circuit precedent establishes that determinations of whether the written description requirement have been met should be consistent with both Federal Circuit precedent and the written description guidelines. *Enzo Biochem, Inc. v. Gen-Probe, Incorporated*, 323 F.3d 956 (Fed. Cir. 2002).

Applicants respectfully refer the Examiner to the USPTO's "Synopsis of Application of Written Description Guidelines" (pertinent pages attached at Appendix B) and in particular to Example 14, pages 53-55. The claim of Example 14 recites a protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A->B. The disclosure of Example 14 provides a single species (SEQ ID NO:3) that has actually been reduced to practice, and describes an assay for identifying the variants having the desired catalytic activity. The analysis considers (1) whether the members of genus vary substantially from each other; and (2) whether the disclosed species is representative of the members of the genus; in order to determine whether one of skill in the art would determine if the applicant was in possession of the necessary common attributes possessed by the members of the genus.

For Example 14, it was determined that the member species did not substantially vary since the variants have 95% identity or greater to the reference sequence, and also possess the catalytic activity. It was also determined that the disclosed species was representative since all members must have at least 95% structural identity to SEQ ID NO:3. The analysis determined that one of skill in the art would conclude that the applicant was in possession of the necessary common attributes possessed by the members of the genus, and therefore the disclosure in this Example meets the written description requirement.

Applicants submit that the Claims directed to the use of a protein encoded by SEQ ID NO:1 and polypeptides that are 70% homologous to amino acids 384-641 of SEQ ID NO.: 1 can be analyzed in a similar manner to that provided in Example 14. First, the polypeptides encoded by the polynucleotides do not substantially vary as members of a genus since they all have at least 70% homology to SEQ ID NO:1 and induce an immune response by NK cells. Second, the polypeptide having SEQ ID NO:1 is a representative species of the genus since all polypeptides must have at least 70% homology to this sequence. Third, variants having the desired activity can be identified by conducting the NK stimulation and cytolytic activity assays described in Examples 1-3 of the specification. Therefore, one of skill in the art would conclude that the Applicants were in possession of the necessary common attributes possessed by the members of the genus, and therefore the instant specification meets the written description requirement for these claims.

Accordingly, it is respectfully submitted that the Claims are supported by an adequate written description and that the Examiner's arguments are both factually and legally flawed. As such, Applicants respectfully request that this ground of rejection be removed.

4. The Claims are Not Anticipated by Srivastava

Claims 50-53, 55, 56 and 58-60 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Srivastava (WO 97/10001). The Federal Circuit has stated the relevant analysis for anticipation as follows:

> A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."

Verdegaal Bros. v. Union Oil Co. Of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

At page 7, last paragraph of the Office Action, the Examiner admits that Srivastava isolated peptide complexes from cells. Thus, Srivastava does not teach the use of isolated and uncomplexed Hsp70 as required by the Claims. As a result, the Claims are not anticipated and Applicants respectfully request that this ground of rejection be removed.

5. The Claims are Not Anticipated by Multhoff

Claims 50-56 and 58-60 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Multhoff et al. (U.S. 6,261,839). At page 8 of the office action, first paragraph, the Examiner admits that Multhoff does not teach the use of isolated Hsp70. Thus, Multhoff does not teach the use of isolated and uncomplexed Hsp70 as required by the Claims. As a result, Claims 50-53, 55-56, and 58-60 are not anticipated and Applicants respectfully request that this ground of rejection be removed.

With respect to Claim 54, the Examiner is evidently applying an anticipation by inherency analysis since Multhoff teaches activation of NK cells by an entirely different method. Applicants submit that NK cells activated by different methods are **inherently different** due to the different activation pathways that are necessarily involved. As the Federal Circuit has held in *Continental Can*:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of

ordinary skill.

Continental Can Company USA, Inc., v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991) (emphasis added) (holding no anticipation due to inherency). Thus, argued gaps in a reference must be filled by evidence that clearly shows the descriptive matter is necessarily present. This is a stringent standard. Indeed, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269 (quoting *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981).

Applicants respectfully submit that the Examiner has provided no evidence that the activated NK cells of Multhoff are the same as the activated cells of Claim 54. Because the Examiner has not met this burden of proof, the rejection cannot stand. Accordingly, Applicants respectfully request that this ground of rejection be removed for Claim 54.

6. The Claims are Not Obvious

Claims 31-37, 39-43, 45-48, 54-56 and 58-60 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Multhoff et al., Blood 86:1374-82 (1995), in view of Srivastava and Multhoff et al., J. Immunol. 158:4341-50 (1997) and the abstract of Boltzer et al., Cell Stress and Chaperones 3:6-11 (1998). A *prima facie* case of obviousness requires the Examiner to provide a reference(s) which (a) discloses all of the elements of the claimed invention, (b) suggests or motivates one skilled in the art to combine the claimed elements to produce the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements precludes a finding of a *prima facie* case of obviousness and without more entitles the Applicants to allowance of the claims in issue. *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990). Applicants respectfully submit that the cited reference neither teach nor suggest each element of the claims. In particular, none of the references teach or suggest use of an isolated and uncomplexed Hsp70 protein, polypeptide, or fragment thereof as indicated by the Examiner at page 13, first full paragraph. Further to this argument, Applicants respectfully direct the Examiner's attention to the two references attached hereto at Tabs 1and 2, respectively. These references, on which Srivastava is listed as an author, teach that HSP peptide complexes may lead to antigen specific cellular response against the peptide chaperoned by the HSPs but not against HSP itself. Thus, these references teach away from the present claims which specify an isolated and uncomplexed Hsp70 protein, polypeptide or fragment. Furthermore, the Examiner's

arguments regarding the effect of the term derivative are now moot. Accordingly, Applicants respectfully request that this ground of rejection be removed and the Claims passed to allowance.

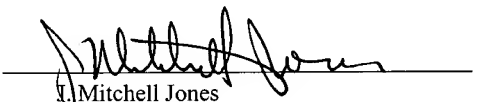
7. The Double Patenting Rejection is Moot

Claims 55 and 56 stand rejected under the judicially created doctrine of double patenting over Claims 19 and 20 of U.S. Pat. No. 6,261,839. It is respectfully submitted that this ground of rejection is rendered moot for the reasons advanced in the preceding paragraph. Thus, Applicants respectfully request that this ground of rejection be removed and the Claims passed to allowance.

CONCLUSION

All grounds of rejection and objection of the Final Office Action of September 29, 2003 (Paper No. 15 in the parent application) having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: January 29, 2004



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